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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
LUCAS, ZACHARIAH	
ART UNIT	**PAPER NUMBER**
1648	

DATE MAILED: 12/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/576,989	RICE ET AL.	
	Examiner	Art Unit	
	Zachariah Lucas	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 August 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-9,12-17,29,61,62,69,70,72,73 and 86* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-9,12-17,29,61,62,69,70,72,73 and 86* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *See Continuation Sheet*.

Continuation of Attachment(s) 6). Other: Claims as renumbered per 37 CFR 1.126.

DETAILED ACTION

1. Currently, claims 1, 3-9, 12-17, 29, 61, 62, 69, 70, 72, 73, and 87 are pending and under consideration in the application.

2. In the prior action, mailed on March 30, 2004, claims 1, 3-6, 9, 12-17, 29, 61, 62, 69, 70, 72, 73, and 87 were rejected, and claims 7, 8, 74, and 75 were objected to. In the Response filed on August 30, 2004, the Applicant amended claim 29, and cancelled claims 74 and 75.

3. The examiner to whom the case has been docketed in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Examiner Zachariah Lucas in Art Unit 1648.

4. Because this action raises new grounds of rejection, the action is being made Non-Final.

Claim Objections

5. **(Prior Objection-Withdrawn)** Claim 29 was objected to for lacking a period at the end of the claim. In view of the amendment of the claim, the objection is withdrawn.

6. **(New Objection)** Claim 13 is objected to because of the following informalities: the claim reads on a mutation within "20 nt" of the ISDR. However, there has been no identification of what an "nt" refers to. It is suggested that a parenthetical - - (nt)- - be inserted after the term "nucleotides" in claim 12 (from which claim 13 depends) to clarify that the term "nt" is referring to nucleotides. Appropriate correction is required.

7. **(New Objection)** The numbering of claims is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not).

Misnumbered claim 87 has been renumbered 86.

Claim Rejections - 35 USC § 101

8. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

9. **(New Rejection)** Claims 69, 70, 72, and 73 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. These claims read on cells comprising a vector. The cells are further described as being human cells. It is noted that the specification indicates that the cells "can be within a non-human mammal." Thus, the specification indicates that it is contemplated that the host cell may be part of a living animal, but does not limit such embodiments to non-human animals. The claims therefore read on a host cell within a human, and on a human. It is suggested that the claims be amended to read on an isolated host cell.

Claim Rejections - 35 USC § 112

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. **(New Rejection)** Claims 15-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. These claims each purport to further limit the polynucleotide claim 11. However, claim 11 has been cancelled from the application. In view of this, it is unclear what polynucleotides claims 15-17 are further describing.

For the purposes of this action, unless otherwise stated, claim 15-17 will be read as though they depended from claim 1 rather than cancelled claim 11.

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. **(New Rejection)** Claims 1, 3-8, 9, 12, 13, 15-16, 29, 61, 62, 69, 70, 72, 73, and 87 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the claimed polynucleotides wherein the adaptive mutation is made to an HCV sequence from a HCV subtype 1b, does not reasonably provide enablement for polynucleotides to any HCV sequence. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. The claims read on non-naturally occurring polynucleotides comprising HCV sequences with an adaptive mutation in the NS5A region that allows the polynucleotide to replicate in a host cell.

In making a determination as to whether an application has met the requirements for enablement under 35 U.S.C. 112 ¶ 1, the courts have put forth a series of factors. See, In re Wands, 8 USPQ2d 1400, at 1404 (CAFC 1988); and Ex Parte Forman, 230 U.S.P.Q. 546 (BPAI 1986). The factors that may be considered include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. Id. While it is not essential that every factor be examined in detail, those factors deemed most relevant should be considered.

The Applicant has identified several alterations to the gene and protein sequences of HCV conferring on vectors with the altered sequences the ability to replicate in cell cultures. See e.g., App., pages 61-62 and Figure 7. However, each of the Examples provided by the Applicant appear to relate to adaptive mutations to a sequence of subtype 1b of HCV. App., page 58, lines 31-33. There are no working examples of adaptive mutations to other NCV subtypes, or any indication that the claimed adaptive mutations would be effective when applied to other HCV subtypes.

The art however indicates that while adaptive mutations such as those claimed have been effective for the adaptation of HCV subtype 1b, such adaptation appears to be "restricted to two subtype 1b isolates." Lanford et al., Virology, 293: 1-9 at page 3, esp., right column end of first paragraph. Additionally, Grobler et al. (JBC 278: 16741-46) teaches that insertion of the adaptive mutation S232I in the NS5A region (corresponding to the claims S1179I mutation of claim 14) was able to confer at least modest replication for an HCV 1b isolate (page 16742). However, the

reference also teaches that the same mutation in an HCV 1a isolate "failed to replicate efficiently in cell culture with the introduction of the single adaptive mutation." Page 16743 See also, page 16744 (teaching that a combination of this mutation with a mutation in the NS3 region "failed to replicate"). Thus, the art indicates that an adaptive mutation for one HCV subtype may be ineffective for another. In particular, the reference demonstrates that the ability of a mutation to produce an adapted phenotype on a subtype 1b HCV was not carried over to a subtype 1a HCV. The reference therefore demonstrates unpredictability in the art of adapting different subtypes of HCV to cell replication even after an adaptive mutation has been determined for a specific subtype. In view of these teachings, and the lack of any demonstration by the Applicant that any of the identified mutations allow adaptation of other HCV phenotypes to replication in cell culture, or guidance towards mutations that would allow culture replication of other subtypes, the Applicant is not enabled for the claimed inventions to the extent that they read on polynucleotides from HCV subtypes other than type 1b.

14. **(New Rejection)** Claims 1, 3-8, 9, 12, 13, 15-16, 29, 61, 62, 69, 70, 72, 73, and 87 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims have been described, generally, above. Claims 7 and 8 additionally require that the polynucleotide is capable of replication in a non-hepatic cell line, especially in HeLa cells. Claims 12 and 13 additionally require that the adaptive mutation is within 20 or 50 nucleotides of an interferon

sensitivity determining region (ISDR). Thus, these claims read on several genera of inventions. The claims are generically drawn to a genus of polynucleotides comprising an adaptive mutation to the NS5A region which allows replication in a cell line. Claims 7 and 8 read on a subgenus that requires the replication to occur in a specific set of cells. Claims 12 and 13 further identify the claims by identifying a region in the NS5A protein where the adaptive mutation is to be found.

The following quotation from section 2163 of the Manual of Patent Examination Procedure is a brief discussion of what is required in a specification to satisfy the 35 U.S.C. 112 written description requirement for a generic claim covering several distinct inventions:

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice..., reduction to drawings..., or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus... See Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406.
>
> A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

Thus, when a claim covers a genus of inventions, the specification must provide written description support for the entire scope of the genus. Support for a genus is generally found where the applicant has provided a number of examples sufficient so that one in the art would recognize from the specification the scope of what is being claimed.

In the present case, the Applicant has provided five working examples of the claimed polynucleotides. See e.g., pages 61-62, and Figure 7. Of these five, only one has been shown to be capable of replication in non-hepatic cells. In each instance, the mutation is either a deletion of an ISDR or found within 20 nucleotides of an ISDR. However, the Applicant has neither

demonstrated that the position of the mutation with relation to the ISDR has any relationship to the mutation's status as an adaptive mutation, nor established any correlation between mutations generally of the NS5A protein/region of the polynucleotide and the status of the polynucleotide as capable of replication in a host cell.

With respect to the claims generally, the Applicant has not demonstrated that any mutation to the NS5A region would result in an adaptive mutation. Thus, the claimed polynucleotides of claim 1 (and its dependant claims) have been identified only by the identification of a desired characteristic of the resultant polynucleotides. According to the law as determined by the Federal Circuit, this is not sufficient description to support a claimed genus. It is noted that the Applicant has identified five adaptive mutations within the NS5A region. However, it is not clear how the identification of five apparently unrelated mutations would support the claims to the genus in view of the uncertainty as to what other mutations would also result in polynucleotides with the desired function. The Applicant has therefore not provided sufficient written description support for the claims as they are drawn to any modification of the NS5A protein that results in an adaptive mutation.

With respect to claims 7 and 8, the Applicant has identified only a single mutation that results in the ability of an HCV polynucleotide to replicate in HeLa cells. The Applicant has identified no other examples of mutations that allow for the replication in non-hepatic cells. Nor has the Applicant drawn any correlation between the desired functional characteristics of the claimed polynucleotides and any known or disclosed structure. The identification of the single species provides no guidance as to the identity of other potential species, nor does it demonstrate

a relationship between mutations of the NS5A protein in general with the ability of the polynucleotide to replicate in non-hepatic cells.

With respect to claims 12 and 13, while the Applicant has identified five mutations that occur within 20 nucleotides of, or involve a deletion of the ISDR, the Applicant has again failed to establish any correlation between the position of the mutation with respect to the ISDR and the adaptive phenotype of the polynucleotide. However, there is no demonstration that any mutation within 20 or 50 nucleotides of the ISDR would result in an adapted phenotype. Thus, the Applicant has identified several species of the claimed invention, but has not established that they are representative of the claimed genus. It is also noted that each of the four mutations that occurs within 20 nucleotides (rather than encompassing the ISDR) occur only to the N-terminal direction of the ISDR. There has been no demonstration that any mutation on the other side of the ISDR would also result in the ability of the mutated polynucleotide to replicate in a host cell.

For the reasons above the indicated claims are rejected for lacking sufficient written description support for the claimed genera of inventions.

15. **(New Rejection)** Claims 7 and 8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the claimed polynucleotides comprising an adaptive mutation in the NS5a, does not reasonably provide enablement for any such polynucleotide wherein the polynucleotide is "capable of replication in a non-hepatic cell," or for embodiments wherein any HCV polynucleotide is capable of replication in a HeLa cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The rejected claims read on the non-naturally occurring HCV polynucleotides of claim 1 further described as "capable of replication in a non-hepatic cell." Claim 8 further identifies the non-hepatic cell as a HeLa cell.

The Applicant has identified several alterations to the gene and protein sequences of HCV conferring on vectors with the altered sequences the ability to replicate in cell cultures. See e.g., App., pages 61-62 and Figure 7. Additionally, the Applicant has demonstrated that HCV type 1b polynucleotides comprising these adaptive mutations were able to replicate both in human hepatic Huh-7 cells, and in HeLa cells. Page 62. However, the Applicant demonstrates that only one of the polynucleotides identified in the application is capable of replication in the non-hepatic cell. Additionally, the teachings of the application are limited to the ability of only adapted HCV type 1b polynucleotides to replicate in these cells. No additional teachings have been made with respect to the adaptation of the claimed polynucleotides to replication on non-hepatic cells.

In contrast to these limited teachings, the Applicant has claimed any polynucleotide comprising an HCV sequence with an adaptive mutation in the NS5A region that is capable of replication in any non-hepatic cells, or any such polynucleotide that is capable of replication in HeLa cells. The teachings in the art tend to indicate that the single example, in the absence of additional guidance, provided by the Applicant is not sufficient to enable those in the art to practice to the full extent as claimed. For example, as was indicated above, the actual examples of the present application appear to be limited to the ability of HCV subtype 1b polynucleotides to replicate in cells. App., page 58, lines 31-33. The teachings in the art relating to the replication of such HCV polynucleotides indicate that colony formation with HCV replicons such as the

claimed polynucleotides is "limited to a single human liver cell line." See e.g., Lanford et al., Virology 293: 1-9 at page 3, esp., right column end of first paragraph. More specifically, the reference also indicates that the ability of the replicons to replicate in human cell lines appears to be limited to the human liver cell line Huh-7.

While the teachings of Lanford demonstrate that those in the art would not have expected any such replicons to work in non-liver cells, the teachings of Zhu et al. (J Virol 77:9204-10) do indicate that those in the art have been able to develop such polynucleotides that replicate in certain non-hepatic cell lines. However, like the present applicant, the authors of this reference were able to achieve replication only in HeLa cells. See e.g., pages 9205. Also, contrary to the claim limitations requiring that the adaptive mutations reside in the NS5A region, the teachings of Zhu indicate that such adaptations appear to occur in the NS4B region. Page 9209. Thus, while the Applicant may have identified a particular sequence that is able to replicate in HeLa cells, it is not clear from the teachings of the application and the art that such is a common characteristic to all polynucleotides capable of replication in non-hepatic cells. From these teachings it appears that, absent demonstration of the replicative ability of a disclosed clone in other non-hepatic cell lines, the Applicant has not provided sufficient information to enable those in the art to make or use polynucleotides capable of replication in any non-hepatic cells.

As was also indicated above, the Applicant has identified only a single embodiment capable of replication in HeLa cells, the polynucleotide with a deletion of the interferon sensitivity determining region (ISDR) in the NS5A region (clone I of the application). The Applicant provides no additional guidance as to what other mutations may result in this ability to replicate in non-liver cells. Further, the teachings of Zhu indicate 1) that not all such adaptive

mutations lie in the NS5A region, and 2) that the identification of such other mutations is difficult and unpredictable. See e.g., pages 4206 and 4209. Because the Applicant has provided little guidance in the identification of such other adaptive mutations, and because the art indicates that the identification of such other mutations has proved elusive and may not involve mutations in the NS5A region, the Applicant is not enabled for the making and use of any polynucleotide comprising an adaptive mutation in the NS5A region that is capable of replication in HeLa cells.

In view of the difficulty faced in the art in deriving HCV polynucleotide adapted for growth in non-hepatic cells lines, and the inability of either the Applicant or those in the art to identify HCV polynucleotides adapted for growth in non-hepatic cell lines other than HeLa cells, the Applicant is not enabled for the claims to the extent that they read on polynucleotides adapted for growth in any non-hepatic cells. Also, because the Applicant has identified only a single mutation in the NS5A region capable of allowing replication in HeLa cells, and the art indicates that the identification of other such adaptive mutations is problematic, and therefore beyond routine experimentation, the Applicant has enabled the making and use of only clone I of the present application as a polynucleotide able to replicate in HeLa cells.

16. **(New Rejection)** Claims 69, 70, 72, and 73 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for isolated host cells comprising the claimed vector, does not reasonably provide enablement for host cells comprised within either the human patient or the transgenic animal fro the reasons set forth below. The instant claims are drawn to host cells prepared by the instant method. The claims are not drawn to isolated host cells, thus, when given the broadest reasonable interpretation, read on host cells comprised within a living organism such as a transgenic animal or a human gene therapy patient. It is noted that the specification contemplates gene therapy on page 30 (lines 25-28) and page 56(lines 10-26); and contemplates transgenic animals on pages 43-44. The specification is not enabling for

host cells comprised within either the human patient or the transgenic animal fro the reasons set forth below.

(A) As drawn to gene therapy

The instant specification does not teach how to overcome problems with in vivo delivery and expression with respect to the administration of the claimed nucleic acids or viral vectors comprising said nucleic acids. The state of the art as of the priority date sought for the instant application is that in vivo gene delivery is not well developed and is highly unpredictable. For instance, Verma et al. (Nature, 1997, Vol. 389, pp. 239-242) teaches that the Achilles heel of gene therapy is gene delivery. Verma et al. state that the ongoing problem is the inability to deliver genes efficiently and to obtain sustained expression (page 239, column 3). Eck et al. (Gene-Based Therapy, In: The Pharmacological Basis of Therapeutics, Goodman and Gilman, Eds., 1996, pp. 77-101) teach that the fate of the DNA vector itself with regard to the volume of distribution, rate of clearance into tissues etc., the in vivo consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA the level of mRNA produced, the stability of the mRNA produced in vivo, the amount and stability of the protein produced and the proteins compartmentalization or secretory fate within the cell are primary considerations regarding effective therapy. Eck et al. state that these factors differ dramatically on the vector used, the protein being produced, and the disease being treated (Eck et al. bridging pages 81-82).

As of the priority date sought, it was well known in the art how to infect or transfect cells in vitro or ex vivo with viral vectors. However, using viral vectors to deliver DNA to an organism in vivo, or using infected or transfected cells to deliver nucleic acids which encode a particular protein sequence to an organism in vivo is in the realm of gene therapy, and as of the priority date sought, highly unpredictable in view of the complexity of in vivo systems. Orkin et al. state ("Report and Recommendation of the Panel to Assess the NIH Investment in Research on Gene Therapy", NIH, 1995) clinical efficacy had not been definitively demonstrated with any gene therapy protocol (page 1, second paragraph). Orkin et al. defines gene therapy as the transfer of DNA into recipient cells either ex vivo or in vivo (page 7, under the heading "Gene transfer"), thus encompassing the instant claims. Orkin concludes that, "none of the available vector systems is entirely satisfactory, and many of the perceived advantages of vector systems have not been experimentally validated. Until progress is made in thee areas, slow and erratic success in applying gene transfer methods to patients can be expected." ID. The authors of Orkin et al. also state that direct administration of DNA or DNA complexes is not well developed and hindered by the low efficiency of gene transfer. Page 8, third full paragraph. The reference teaches that adequate expression of the transferred genes is essential for therapy, but that (in 1995) current data regarding the level and consistency of expression of transferred genes in animal models was unknown. Orkin et al. states that in protocols not involving ex vivo infections/transfection, it is necessary to target the expression of the transferred genes to the appropriate tissue or cell type by means of regulatory sequences in gene transfer vectors. The specification does not teach a vector having a specific regulatory sequence which would direct the expression of the nucleic acids within the appropriate tissue type.

The specification does not remedy any of the deficiencies or the prior art with regard to gene therapy. Given the lack of any guidance from the specification on any of the above issues pointed out by Verma or Eck or Orkin. One of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to practice the methods of claims.

(B) As drawn to a transgenic animal

The specification states on pages 52-54 that genetically engineered host cells can be used to produce transgenic non-human animals. The specification does not provide guidance in the making of a transgenic animal comprising the instant recombinant polynucleotides or transformed cells. In the art of producing transgenic animals, the phenotype of the resultant transgenic animal is not always predicable or viable. The vectors to be used for directing the expression of transgenic in a given tissue or in all tissues must contain the appropriate regulatory regions (Houdebine, Journal of Biotechnology, 1994, Vol. 34, pp. 269-287), see bridging pages 272-273) and expression is heavily dependent on the site of integration in the host genome, and the site of integration is presently unpredictable (Houdebine, page 277, column 1). Therefore, it is concluded that one of skill in the art would undergo undue experimentation in order to make a transgenic animal comprising the claimed host cells.

Amendment of the claims to read on "An isolated host cell" would overcome this rejection.

Claim Rejections - 35 USC § 102

17. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

18. **(Prior Rejection-Maintained)** Claims 1, 61, 62, 70, 72, 73, and 87 were rejected under 35 U.S.C. 102(e) as being anticipated by Bartenschlager et al., (U.S. 6,630,343). These claims read on a polynucleotide encoding a non-naturally occurring HCV sequence capable of

reproductive replication in a host cell, or capable of being transcribed into a HCV sequence that is capable of productive reproduction is a host cell, wherein the polynucleotide comprises "from 5' to 3' on the positive-sense nucleic acid, a functional 5' non-translated region (5' NTR); one or more protein coding regions, including at least one polyprotein coding region that is capable of replicating HCV RNA; and a functional HCV 3' non-translated region (3' NTR), wherein said polynucleotide further comprises an adaptive mutation in the NS5A coding region that confers improved cell culture characteristics to said polynucleotide." The dependant claims read on vectors and host cells comprising such a polynucleotide.

The Applicant traverses the rejection based on the assertions in a submitted declaration under 37 CFR 1.131 naming Dr. Keril J. Blight as the declarant. This argument is not found persuasive because the Declaration has not been considered by the Office. The declaration has not been executed by the declarant. The rejection is therefore maintained.

Claim Rejections - 35 USC § 103

19. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

20. **(Prior Rejection- Maintained in part)** Claims 3-6, 12-17, and 29 were rejected under 35 U.S.C. 102(e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Bartenschlager as applied against claims 1, 61, 62, 70, 72, 73, and 87. The Applicant traversed

this rejection on the same grounds as presented with respect to the anticipation rejection over Bartenschlager above. As the declaration has not been properly executed, the arguments are not found persuasive.

However, the rejection is withdrawn from claims 14 and 17 as there does not appear to be any specific guidance or suggestion in the reference or in the art to suggest the modification of the HCV NS5A protein at the sites indicated by these claims.

The rejection is therefore maintained against claims 3-6, 12, 13, 15, 16, and 29.

21. **(Prior Rejection- Maintained)** Claim 9 was rejected under 35 U.S.C. 103(a) as being unpatentable over Bartenschlager as applied above. The Applicant traversed this rejection on the same grounds as presented with respect to the anticipation rejection over Bartenschlager above. As the declaration has not been properly executed, the arguments are not found persuasive. The rejection is therefore maintained.

Conclusion

22. No claims are allowed.

23. It is noted that, because claims 14 and 17 refer to specific sequences from HCV subtype 1b, the claims are read as being limited to HCV polynucleotides in such viruses.

24. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachariah Lucas whose telephone number is 571-272-0905. The examiner can normally be reached on Monday-Friday, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 571-272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Z. Lucas
Patent Examiner

JAMES HOUSEL 12/13/04
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600